EXHIBIT 1

June 19, 2015

Supplement to Expert Witness Report of Godfrey P. Oakley, Jr. MD, MSPM

I. Introduction

I have been asked to provide a supplemental report to identify and further explain certain opinions that I previously provided in my expert report dated October 1, 2014 and in my deposition and trial testimony in the D.W.K. and Schmidt trials. This report supplements my prior expert report dated October 1, 2014.

II. Summary of Opinions

In short, I conclude that valproic acid causes spina bifida. I conclude that first semester exposure to valproic acid increases the risk of spina bifida by 20.6 fold or 2060 percent compared to the general population.[1] I conclude that the 1982 Dear Doctor Letter and the valproic acid package insert should have included the 20.6 fold increased risk of spina bifida from first trimester exposure to valproic acid. I conclude that this risk is high enough and serious enough that Abbott should have taken steps to limit the use of valproic acid to the absolute minimum number of women of reproductive age and to minimize pregnancies among women taking valproic acid. I conclude that Abbott did not attempt to limit the use of valproic acid in women of reproductive age given that, after it knew valproic acid was a very serious and powerful cause of birth defects in human beings, it sought approval to market the drug for other indications that affect women of reproductive age and sold the drug for those indications when approved. I conclude that Abbott did not encourage women of reproductive age to use effective contraceptives if they were taking valproic acid. I also conclude that registries of pregnant women exposed to valproic acid were capable of being initiated and should have been initiated at the time valproic acid was first

marketed. Furthermore, pregnancy registries and further studies were capable of being initiated and should have been established in 1982 following the information discussed below relating to valproic acid and spina bifida. The exposure registries would have confirmed the increased risk for spina bifida and would have provided the opportunity to learn sooner of other adverse effects of in utero exposure to this drug such as the increased risk for major congenital malformations and a reduction in cognitive abilities. I further conclude that mandatory folic acid fortification required by the FDA by January 1, 1998, was likely preventing most, if not all, folic acid-preventable spina bifida by January 1, 1999.[2] Folic acid supplements are not effective in preventing spina bifida caused by valproic acid.[3]

III. Background Information

A. Background on spina bifida

Spina bifida is a serious birth defect that develops in the first 28 days after the sperm meets the egg.[4] It is an error in the development of the neural tube that closes zipper-like from mid body to head and to rump. If the zippering process does not work toward the head, anencephaly develops and if the zippering fails towards the rump, spina bifida develops. The amount of disability from the spina bifida is determined by where the spina bifida occurs. The closer to the head, the more the paralysis, but even the lower levels are associated with paralysis of bladder and bowel function. One way to consider the effect is to consider that a neural tube is developing fine, but the drug valproic acid disrupts that process. The effect on the baby will be determined by where the damaged spinal cord starts. Because spina bifida develops in the first 28 days after the sperm meets the egg, spina bifida often occurs before a woman knows that she is pregnant. Spina

bifida caused by valproic acid may present with or without other symptoms of valproic acid exposure.

B. Background on folic acid

Folic acid is a vitamin that decreases folic acid-preventable spina bifida by up to 75%. In 1996, the FDA put out a rule that required manufacturers of enriched flour to include folic acid. Folic acid fortification prevents approximately 1,300 cases of spina bifida a year in the United States.[2] By January 1, 1999, mandatory folic acid exposure was likely preventing most, if not all, folic acid-preventable spina bifida. Folic acid fortification, however, is not effective in preventing spina bifida caused by valproic acid.[3]

C. Background on the seriousness of valproic acid

As I testified during the Schmidt trial, valproic acid is in the top three drugs (thalidomide, Accutane, and valproic acid) for causing life-altering, serious birth defects among all drugs on the market in the United States.

IV. Abbott inadequately responded to learning that valproic acid causes spina bifida in children: Abbott did not include the increased relative risk, did not advise women taking the drug to avoid pregnancy in the 1982 Dear Doctor Letter or package insert, and failed to start a pregnancy registry.

A. The importance of odds ratio/relative risk to communicate risk.

The original MMWR article showing that valproic acid-caused spina bifida communicated this risk in two ways.[1] First, it reported the 20.6 odds ratio or increase in risk for spina bifida among women who took valproic acid in the first trimester. The routine analysis of case control data produces an odds ratio or an approximation of the relative risk. Case control studies do not provide an estimate of absolute risk in those exposed. To make an estimate of the absolute risk among those exposed requires having an estimate of incidence or prevalence from a separate

study. Once there is an estimate of incidence with no exposure, the incidence with exposure is estimated by multiplying by the odds ratio. The MMWR multiplied the 20.6 increased risk times incidence/prevalence of spina bifida observed in metropolitan Atlanta—1 per 1000 resulting in an estimate of 1 to 2 per cent. Although this was a reasonable estimate, it takes a cohort/exposure pregnancy registry design to have a direct estimate of relative risk. The importance of including the absolute risk in the MMWR statement was to give advice to women who were on valproic acid and contemplating an abortion because of the high relative risk. This absolute risk was also intended to discourage women from suddenly stopping the use of the drug without proper counsel from their physician.

Thus a reasonable conclusion is that valproic acid exposure in early pregnancy caused more than a 20.6 fold or 2060 percent increase in risk for a very serious, life altering birth defect—spina bifida. This is a very high risk and is one that should be known by physicians and patients as drugs are selected to treat an individual. It would be expected that the understanding of this very high risk would discourage use of the drug by both physicians and patients. The average physician would unlikely know the incidence of spina bifida. Without knowing that number, he or she would not be able to calculate the 20.6 fold increased risk by applying the spina bifida absolute risk of one to two percent. Abbott should have included the 20.6 increased risk for spina bifida caused by valproic acid as well as included the absolute risk in order to make the risk clear to the doctor and the patient.

I have been asked in a deposition and in a trial if Abbott's accepting as causal the data from Lyon was a responsible act. It was an important first step. How can one implement an effective prevention policy if one does not accept that its drug causes a serious problem like spina bifida? In my opinion, patients and physicians considering the use of or using valproic should know both

the odds/ratio relative risk as well as the absolute risk. If a patient is not on valproic acid, I would argue it is more important to know the relative risk. The relative risk for spina bifida from first trimester exposure is high—like the risk of lung cancer from smoking 2 packs of cigarettes a day is high. Public health messages to discourage smoking talk about the 20 fold increase risk for lung cancer, not the absolute risk of lung cancer from smoking. If one wants to clearly communicate risk, one includes the relative risk. In my opinion, Abbott should have included the relative risk in its 1982 Dear Doctor Letter and in the package insert.

Abbott should have also taken steps to minimize the use of valproic acid and to minimize pregnancies among reproductive aged women taking the drug. I believe that having this drug approved for other conditions that women of reproductive age have resulted in more women having babies with spina bifida caused by valproic acid. Abbott did not encourage or require women of reproductive age to take contraceptives to prevent pregnancy while on the drug. Given that premarket testing of a possible new drug that shows the drug causes birth defects in animals usually leads to a company not bringing a drug to the market, it is very curious that Abbott didn't do all it could to minimize the use of valproic acid once it knew not only that the drug caused birth defects in animals, but also in human beings.

B. Importance of pregnancy exposure registries to drug safety

Registries of women exposed to a drug in pregnancy are an important part of the safety net for protecting children from birth defects and other adverse effects from exposure while they develop in their mothers' uteruses. It is, therefore, important to understand how drugs are regulated for safety and some of the history of how we got the regulations we now have.

i. The Thalidomide epidemic of severe birth defects:

In the late 1950s and early 1960s there was an epidemic of severe birth defects caused by the sleeping pill thalidomide. The epidemic was generally viewed as a failure of government drug regulations. Following the discovery of the cause of the epidemic, drug regulations were remarkably changed in the United States and many other countries. To seek to protect human fetuses, the government required that all drugs be screened for the risk of birth defects by giving the drug to pregnant animals. I wrote an article in the late 1970s suggesting that we did not know if such screening actually prevented drugs that would cause birth defects from coming to the market, but such screening might have, as there had been no recent epidemics of birth defects from exposures to new drugs.

Concurrently, many countries established birth defects surveillance systems in order to try to identify epidemics of birth defects, and if they were to occur, to begin studies to find the causes of the epidemics. It was the Lyon, France, birth defects registry and exposure data collected that provided scientists the opportunity to test the hypothesis that valproic acid causes spina bifida. The hypothesis was raised by Dr. Robert, who was studying exposures in pregnancy among children with spina bifida as they were discharged from the local neurosurgical hospital. The hypothesis was raised by this alert practitioner who just happened to work for the birth defects registry and knew the reporting form included questions about whether or not the mother of the baby was consuming drugs for epilepsy. She then set out to analyze the data that had been collected and found the remarkable 20.6 fold increased risk that made it highly likely that valproic acid causes spina bifida.

The research in Lyon proved the value of having birth defects registries in identifying new drugs causing birth defects. It also pointed out a major shortcoming of the regulations: no pregnancy

registry of women of reproductive age was established by the manufacturers when valproic acid was first marketed. The studies that show a drug works and is safe are carried out in men, or women who cannot get pregnant. Thus all drugs come to the market without exposures of pregnant women to the drug. Because safety has not been demonstrated, there is a need for pregnancy registries. Registries of exposed pregnant women, beginning at the time of marketing, would provide the opportunity to discover developmental problems in exposed fetuses that a drug may cause earlier than would likely be discovered by an alert clinician or an outcome registry such as a birth defects registry.

ii. Thalidomide identified as a cause of birth defects in a pregnancy registry

McBride in Australia reported an excess of birth defects among the children born to women whom he had given the drug in pregnancy in a clinical trial to determine whether or not it was effective in morning sickness.[5, 6] He learned this adverse risk within two years of starting the study. While it is true that what he discovered was a very unusual birth defect which was highly visible, severe and occurred at a high rate, he did demonstrate the effectiveness of pregnancy registries in identifying the most severe and frequent birth defects in a relatively short period of time. Lenz reached his decision regarding thalidomide as the cause of birth defects because an epidemic was recognized some 6 years after the drug was marketed.[6, 7] He eventually developed the idea that it might be the new drug thalidomide that caused the epidemic and then proved it. Thus the pregnancy registry used in Australia identified the drug as a cause of major and severe birth defects in about 2 years. Had a pregnancy registry been set up with marketing of thalidomide it is likely that the adverse effect of the drug would have been would have been found earlier than it was actually found by waiting for enough cases to occur for a scientist to suspect it was a new drug causing the problem.

C. Could a pregnancy registry have been established in 1982?

There is evidence that strongly suggests a registry of pregnant women exposed to valproic acid could have been set up in in 1982 as I noted in my report dated October 1, 2014. There is some additional evidence that supports my conclusion that Abbott could have established a registry of pregnant women exposed to valproic acid.

Omtzigt and colleagues established a pregnancy registry of women with epilepsy beginning in November 1, 1985 to investigate pregnancies of women treated with anti-epileptic drugs.[8] They reported on the results thorough July 4, 1990—about 4 and a half years. It registered 297 pregnancies with 303 fetuses among 261 different women. 9 of 96 exposed to valproic acid had fetuses with birth defects or 9.4%. 6 of the birth defects were spina bifida, resulting in a 6.3% prevalence rate. None of the other 207 women on other antiepileptic drugs had a child with spina bifida. This was a highly statistically significant result with a p value of 0.0003. Thus this pregnancy registry, set up in 1985, of women treated with antiepileptic drugs showed in less than 5 years that there was a major increase in spina bifida. They also showed the value of information from a pregnancy exposure cohort or registry. They confirmed the very large increase in risk for spina bifida among fetuses exposed to valproic acid in early pregnancy. In addition they had a direct estimate of absolute risk among exposed women of about 6% which was larger, 3 to 6 times larger, than had been estimated in the MMWR 1982 report from Lyon.

Abbott did participate, along with others, in supporting a pregnancy registry in 1996. The observations from that registry were provided to Abbott in 2002 and were published in 2005.[3, 9] The observations from that registry would have been available to Abbott much sooner if it had taken steps to initiate a registry in the early 1980s.

These results support my opinion that Abbott could have set up a pregnancy registry in 1982 as well as in 1978. It was done in the Netherlands at a university. It could have been done in the United States, too. It could also have included women treated with other anticonvulsants for comparison. Such a registry would have confirmed the increased risk for spina bifida and would have provided the opportunity to learn sooner of other adverse effects of in utero exposure to this drug such as the increased risk for major congenital malformations, reduction in cognitive abilities, and other developmental problems.

The Omtzigt et al. paper provides strong support for the conclusion that it was feasible to have established a pregnancy cohort study of women exposed to anticonvulsant drugs in the early 1980s.[8] They did it. It was not just birth defects that were studied in registries and epidemiological studies. As I included in my report dated October 1, 2014, the effective atomic bomb registry and lung cancer and smoking studies are evidence that it was feasible to establish a pregnancy registry in 1982.

Burroughs Wellcome, a drug company, established the Acycolvir Pregnancy Registry around 1984 to help evaluate the safety of this new drug in pregnancy.[10] Thus, this drug company concluded that there were epidemiological techniques available that would permit the evaluation of its new drug using the pregnancy registry approach.

Glaxo Smith Kline established a pregnancy registry in 1992 for its new antiepileptic drug, Lamotrigine, to determine the incidence of birth defects among women exposed in pregnancy. [11] Over the next 18 years they enrolled 3,416 lamotrigine-exposed pregnancies that had been prospectively enrolled from 43 countries. 2,444 had known outcomes and 972 had been lost to follow-up. 1817 of the infants had been exposed to lamotrigine monotherapy, 173 to poly-

therapy that included valproate, and 502 to poly-therapy without valproate. Major congenital anomalies occurred in 2.2% of those exposed to mono-therapy, in 10.7% in those with poly-therapy that included valproate, and in 2.8% of those exposed to poly-therapy that did not include valproic acid. This registry succeeded and produced data that is consistent with the fact that women who take valproic acid while pregnant have a 3-4 fold increase in major congenital malformations. The epidemiological techniques used in the study are similar to those used in the Acyclovir registry. Thus I conclude that, in 1982, it was certainly possible to establish a pregnancy registry for women exposed in pregnancy to valproic acid, and that such studies would have provided an avenue to obtain data on other developmental anomalies caused by valproic acid exposure beyond spina bifida.

As discussed above, Omtzigt et al. instituted a registry like Abbott could have done.[8] Other registries also demonstrate the feasibility of an Abbott-funded registry. For instance, in the 1960s, thalidomide was shown to cause severe birth defects in the clinical trial run by McBride. The data from these registries show that a pregnancy registry for valproic acid was possible in 1982. It is difficult to understand, knowing that the drug caused birth defects in animals, that Abbott did not establish such registries. Abbott's only barrier to establishing a registry was a lack commitment and money to establish such a registry. There were no other barriers.

V. Conclusion

It is surprising that Abbott did not start a pregnancy registry in 1982 since it planned to keep the drug on the market. If a drug is known to cause one developmental problem, it would be at high risk for causing other developmental problems, such as other birth defects, reduction in cognitive function, and/or autism. Had Abbott set up an exposure registry, it is likely it would have

discovered that valproic acid causes over developmental problems sooner than those problems were actually found. I conclude that the 1982 Dear Doctor Letter and the package insert should have included the 20.6 fold increased risk of spina bifida from first trimester exposure to valproic acid. I conclude that the risk is high enough and serious enough that Abbott should have taken steps to limit the use of this drug to the absolute minimum number of women of reproductive age and minimize pregnancies among women taking valproic acid by advising women taking valproic acid to be on effective birth control.

VI. Supplemental Disclosures

Since my October 1, 2014 report, I have testified, in deposition or trial, in the following matters:

D.W.K. v. Abbott Laboratories Inc., 13-cv-326, In The United States District Court for the Southern District of Illinois (deposition and trial);

J.B. v. Abbott Laboratories Inc., 13-cv-326, In The United States District Court for the Southern District of Illinois (deposition);

E.P. and C.P. v. Abbott Laboratories Inc., 13-cv-326, In The United States District Court for the Southern District of Illinois (deposition);

Schmidt v. Abbott Laboratories Inc., 1222-CC02479-01, In The Circuit Court of Missouri (deposition and trial);

B.F. v. Abbott Laboratories Inc., 4:12-cv-01760-CAS, In The United States District Court for the Eastern District of Missouri (deposition).

Respectfully,

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Citations

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